Bifunctional nanoparticle assemblies: photoluminescent and nitric oxide photodelivering monolayer protected platinum clusters

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In this contribution the design and fabrication of bifunctional, photoresponsive hybrid metal nanoparticle assemblies is reported. Integration of tailored porphyrin and NO photodonor units into *ca.* 1 nm carboxy-terminated platinum induces the formation of particle nanoassemblies of *ca.* 10 nm, which are quite soluble in aqueous solution at physiological pH and exhibit a bichromophoric behavior. Direct monitoring of NO through an ultrasensitive NO electrode demonstrates that the nanoparticles are stable in the dark but supply NO at nanomolar level in a way exclusively regulated by light excitation. Besides, the typical red fluorescence arising from the porphyrin centers in the nanoassembly is not quenched extensively, offering a useful tool for mapping the localization of the nanoparticles in bio-environments. Overall these nanohybrids represent appealing *bright point sources* of NO to be tested in biological research in the perspective of practical application in the emerging field of nanomedicine.

Introduction

Nitric oxide (NO), an ephemeral diatomic inorganic radical, occupies definitely a relevant place in the fascinating realm of biologically important molecules. The combination of properties such as relatively long half-life in biological systems (*ca.* 5 s), diffusional radius in the range of 40–200 μm, lipo-solubility, absence of charge and small molecular size, make NO a key bioregulator of important physiological processes[1] encompassing neurotransmission, vasodilatation and hormone secretion in living bodies.[2] Furthermore, NO is an effective sacrificial antioxidant in the free radical-induced lipid oxidation[3] and a promising anticancer agent.[4] This multifaceted role of NO has stimulated an explosion of interest in recent years in designing compounds able to deliver this species for potential therapeutic applications.[5] At this regard, the accurate regulation of the NO dosage is a key issue. In their excellent review Wang and coworkers outlined that NO can actually act as a *double-edge sword* being either beneficial or detrimental depending on the doses.[6] Light represents one of the most elegant and non-invasive on/off triggers for the rapid and controlled introduction of NO in biological systems. Therefore, compounds photochemically active to supply NO are much more desirable if compared to those based on either spontaneous thermolysis or metabolic transformation.[7] Integration of NO photodonors in appropriate materials, is very important in the perspective of practical applications. However, only a limited number of examples have addressed this issue to date.[8] We have recently contributed to this fascinating research field by developing a variety of NO photoactivable systems. They include mono- and multilayer films,[9,10] DNA intercalators,[11] amphiphilic nanoassemblies,[12] and metal nanoparticles.[13] In this context, thiol-stabilized metal nanoparticles, often referred to as monolayer-protected clusters (MPCs), are particularly suited for bio-applications.[14] Their small sizes and the modification of their surface by the introduction of tailored functional units lead to intriguing nanohybrids which are evincing widespread interest in biomedicine, spanning from biosensing to drug delivery.[15] In our preliminary communication we have reported on the light-regulated release of NO from water soluble platinum nanoparticles.[13] This work encouraged us to explore the possibility to create MPCs which combine *NO photorelease* to *photoluminescence* properties. Such a system would represent a significant step forward in the perspective of practical applications, due to the great potential that luminescence offers in mapping the particles localization in bio-environments. With this in mind, in this paper we report the design and fabrication of water soluble platinum nanoclusters decorated with tailored NO photodonor and porphyrin units which exhibit water solubility, relatively small sizes, photocontrolled NO release and satisfactory fluorescence yield.

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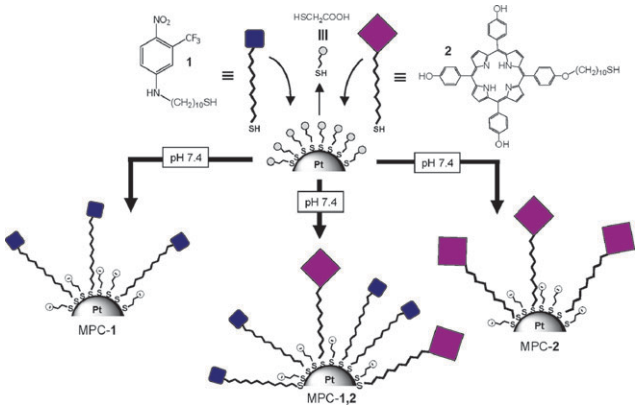
Experimental

Synthetic procedures

All syntheses were carried out under a low intensity level of light. The NO-photodonor **1** (Scheme 1) was synthesized according to our recently reported procedure.[13] The porphyrin derivative **2** (Scheme 1) was prepared in a three-step synthesis illustrated in the following.

4,4′,4″-(20-{4-[(10-Iododecyl)oxy]phenyl}porphyrin-5,10,15-triyl)triphenol (2a). 5,10,15,20-Tetra(4-Hydroxyphenyl)-porphyrin (0.130 g, 0.191 mmol) and sodium carbonate (0.073 g, 0.5 mmol) were refluxed in 500 mL of acetonitrile under argon flux for 45 min. Afterwards, diiododecane (0.3 g, 0.764 mmol) were added and the final solution was refluxed for 2 days. The reaction mixture was then filtered and washed with



Scheme 1 Schematic representation of the functionalization of the carboxy-terminated MPC with **1**, **2** or both to obtain the corresponding MPC-**1**, MPC-**2** and MPC-**1,2**.

acetonitrile. The organic solution was concentrated under reduced pressure and purified by column chromatography (dichloromethane–methanol, 9:1) to give **2a** (yield 15%). Anal. calc. (%) for $C_{54}H_{49}N_4O_4I$ (944.91): C, 68.64; H, 5.23; N, 5.93; found: C, 68.61; H, 5.15; N, 5.87; ESI-MS *m*/*z*: $[M + H]^+$ 945.9; $[M + Na]^+$ 967.9; ^{1}H-NMR 200 MHz, CD_3OD, δ 1.29 (m, 12 H, O–CH_2–CH_2–$(CH_2)_6$–CH_2–CH_2–I), 1.74 (m, 4 H, O–CH_2–CH_2–$(CH_2)_6$–CH_2–CH_2-I), 3.17 (*t*, 2 H, J = 5.9 Hz, CH_2–I), 3.96 (*t*, 2 H, O–CH_2–), 7.04 (d, 2 H, J = 8.4 Hz, phenyl), 7.18 (d, 6 H, J = 8.2 Hz, phenyl), 7.86 (d, 2 H, J = 8.6 Hz, phenyl), 7.97 (d, 6 H, J = 8.4 Hz, phenyl), 8.85 (s broad, 8 H, β-pyrrole).

S-(10-{4-[10,15,20-*tris*(4-Hydroxyphenyl)porphyrin-4-yl]-phenoxy}decyl)ethanethioate (2b). A mixture of **2a** (0.09 g, 0.1 mmol) and MeCOSK (0.12 g, 1 mmol) in acetonitrile–methanol (8:2) (500 mL) was refluxed for 6 h under constant flux of argon. After cooling down to ambient temperature, the solvent was distilled off under reduced pressure. The residue was suspended in CH_2Cl_2 and filtered. The organic solution was concentrated under reduced pressure and purified by column chromatography (dichloromethane–cyclohexane, 9:1) to give **2b** (yield 85%). Anal. calc. (%) for $C_{56}H_{52}N_4O_5S$ (893.12): C, 75.31; H, 5.86; N, 6.27; S, 3.59; found: C, 74.93; H, 5.55; N, 6.15; S, 3.68. ESI-MS *m*/*z*: $[M + H]^+$ 894.1; $[M + Na]^+$ 916.1; ^{1}H-NMR 200 MHz, CD_3COCD_3, δ 1.38 (m, 12 H, O–CH_2–CH_2–$(CH_2)_6$–CH_2–CH_2–$SCOCH_3$), 1.57 (m, 2 H, O–CH_2–CH_2), 1.94 (m, 2 H, CH_2–CH_2–$SCOCH_3$), 2.28 (s, 3 H, CH_3), 2.9 (t, 2 H, CH_2–S), 4.3 (*t*, 2 H, CH_2–O), 7.3 (m, 8 H, phenyl), 8.1 (m, 8 H, phenyl), 8.9 (s, 8 H, β-pyrrole).

4,4′,4″-(20-{4-[(10-Mercaptodecyl)oxy]phenyl}porphyrin-5,10,15-triyl)triphenol (2). Acetyl chloride (100 μl, 1.4 mmol) was added dropwise to a solution of **2b** (42 mg, 0.05 mmol) in methanol (50 mL) maintained at −78 °C under N_2. After 15 min, the mixture was allowed to warm up to ambient temperature in 3 h. The solvent was distilled off under reduced pressure to afford **2**. Anal. calc. (%) for $C_{54}H_{50}N_4O_4S$ (851.08): C, 76.21; H, 5.92; N, 6.58; S, 3.77; found: C, 76.55; H, 5.86; N, 6.62; S, 3.83. ESI-MS *m*/*z*: $[M + H]^+$ 852.1; $[M + Na]^+$ 874.1; ^{1}H-NMR 200 MHz, CD_3COCD_3, δ 1.40 (m, 12 H, O–CH_2–CH_2–$(CH_2)_6$–CH_2–CH_2–$SCOCH_3$), 1.56 (m, 2 H, O–CH_2–CH_2), 1.97 (m, 2 H, CH_2–CH_2–$SCOCH_3$), 2.88 (*t*, 2 H, CH_2–S), 4.32 (t, 2 H, CH_2–O), 7.3 (m, 8 H, phenyl), 8.1 (m, 8 H, phenyl), 8.9 (s, 8 H, β-pyrrole).

Nanoparticles preparation

The carboxy-terminated Pt nanoparticles were prepared according to our recently reported synthetic protocol.[16] Introduction of the chromogenic thiols **1**, **2** or both to obtain MPC-**1**, MPC-**2** and MPC-**1,2** was achieved through the place-exchange method.[14,17] Specifically, the carboxy-terminated Pt nanoparticles in the protonated form were dissolved in acetonitrile solutions of **1** (500 μM), **2** (25 μM) or both (in a molar ratio 20:1) and incubated under stirring for different times at room temperature. Afterwards the solvent was removed by rotary evaporation under vacuum, and the nanoparticles were redispersed in water at pH 7.4. The unbound **1** and **2**, totally insoluble in water medium, were removed through a few cycles of redispersion–centrifugation. The absence of the free compounds was checked by TLC analysis and the extent of the exchange reaction was easily monitored by UV-Vis absorption spectroscopy.

Instrumentation

UV/Vis absorption spectra were recorded with a Jasco V 560 spectrophotometer. Fluorescence emission and excitation spectra were recorded with a Spex Fluorolog-2 (mod. F-111) spectrofluorimeter. The fluorescence quantum yield was obtained using 5,10,15,20-tetra(4-hydroxyphenyl)porphyrin in methanol as standard (Φ_F = 0.13).[18] The absorbance value of the solutions at the excitation wavelength were lower than 0.15 for 1 cm pathlength.

Dynamic light scattering (DLS) measurements were performed with a Horiba LS 550 apparatus equipped with a diode laser with a wavelength of 650 nm.

NO release was measured with a World Precision Instrument, ISO-NO meter, equipped with a data acquisition system, and based on direct amperometric detection of NO with short response time (<5 s) and sensitivity range 1 nM–20 μM. The analog signal was digitalized with a four-channel recording system and transferred to a PC. The sensor was accurately calibrated by mixing standard solutions of $NaNO_2$ with 0.1 M H_2SO_4 and 0.1 M KI according to the reaction:[19]

$$4H^+ + 2I^- + 2NO_2^- \rightarrow 2H_2O + 2NO + I_2$$

The NO photorelease experiments were performed by irradiating the samples in a thermostated quartz cell (1 cm pathlength, 3 ml capacity) using the monochromatic radiation at λ_{exc} = 400 nm of a fluorimeter Fluorolog-2 (mod. F-111). NO measurements were carried out with the electrode positioned outside the light path in order to avoid false NO signal due to photoelectric interference on the ISO-NO electrode.

The quantum yield for NO photogeneration was determined by using the following equation:

$$\Phi = \Delta[NO]V/\Delta t I_0 F$$

where $\Delta[NO]/\Delta t$ is the rate of NO formation, V is the volume of the irradiated solution, I_0 is the intensity of the incident

photons and F is the fraction of the photons absorbed by MPC-**1**,**2** at the excitation wavelength.

Results and discussion

Synthesis and characterization of platinum nanoparticles

One of the main pre-requisite for bio-applications of nanoparticles is their solubility in water medium with preservation of their physicochemical properties over the time. We have recently reported a simple, light-assisted synthetic protocol to obtain ultrasmall (*ca.* 1 nm), water soluble and stable platinum nanoparticles protected with a monolayer of thioglycolic acid, in a single reaction step.[16] These carboxy-terminated metal nanoparticles represented suitable scaffolds to fabricate the NO photoreleasing MPC-**1** by introduction of the NO photodonor **1** with self-assembling characteristics through place-exchange reaction (Scheme 1). Thiol **1** integrates a commercial nitroaniline derivative that we have discovered to be a NO-caged compound which satisfies several prerequisites for bio-applications.[20] Actually, it combines dark stability, adequate absorption coefficient at wavelengths longer than 350 nm, photorelease of NO (*via* nitro-to-nitrite photorearrangement) under the exclusive control of light inputs and generation of non-toxic reaction intermediates. The strategy we adopted to obtain fluorescent, NO photoreleasing MPCs, was that to decorate the surface of the NO photoreleasing nanoparticles with a certain number of fluorescent unit by place-exchange reaction. To this end, we have designed and synthesized the porphyrin derivative **2** with self-assembling characteristics. Our choice to use a porphyrin center as suited fluorogenic unit was motivated by the following reasons: (1) it is well known that, unlike their bulk counterparts, metal nanoparticles do not quench the fluorescence of porphyrins intensively;[21] (2) our recent work on a photoactivable, non-covalent amphiphilic nanoassembly based on porphyrins and the same NO photodonor unit of **1**, demonstrated that these chomophores exhibit an independent photochemical behavior due to the absence of both energy and electron transfer processes between the two chomogenic units in the nanoassembly;[12] (3) the fluorescence of porphyrins falls in the red-region of the electromagnetic spectrum, highly desirable for bio-applications.

MPC-**1**,**2** and, for comparison, MPC-**1** and MPC-**2** (Scheme 1) were prepared by place-exchange reaction (see Experimental section for details). The intense absorption of thiols **1** (at 380 nm) and **2** (at 424 nm), together with the weak, structureless surface plasmon absorption of the Pt nanoparticles in the same spectral region[22] (see Fig. 1) offer the ideal conditions to follow the course of the exchange reaction simply by UV-Vis absorption. Fig. 1 shows the absorption spectrum at pH 7.4 after incubating the carboxy-terminated Pt nanoparticles with a mixture of **1** and **2** in a molar ratio 20 : 1 for 30 min. This ratio was chosen in order to obtain a comparable absorption of the two chromophoric units in the 380–430 nm region. The molar absorbtivity of **1** at 380 nm is in fact *ca.* 10-fold smaller than that of **2** at 424 nm. It can be promptly noted that, after the exchange reaction, the metal nanoparticles exhibit the typical absorption band of **1** at *ca.*

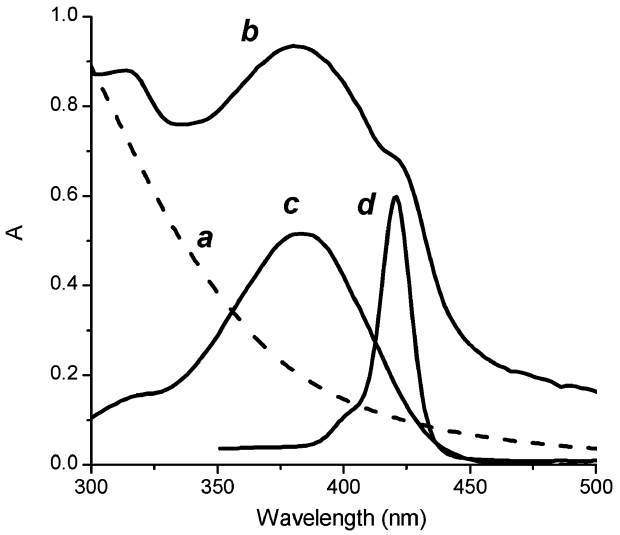


Fig. 1 Absorption spectra of the carboxy-terminated Pt nanoparticles before (a) and after (b) place exchange reaction with a mixture of **1** and **2** in molar ratio 20 : 1 for 30 min and subsequent redispersion in water at pH 7.4. The absorption spectra of the free **1** (c) and **2** (d) in methanol solution are also shown, for sake of comparison.

380 nm and a clear shoulder in the correspondence of the Soret absorption of the porphyrin **2** at *ca.* 420 nm, in addition to the Pt surface plasmon absorption. Since thiols **1** and **2** are not soluble in aqueous medium, these observations provide unambiguous evidence for their partial incorporation into the carboxy-terminated Pt nanoparticles to give MPC-**1**,**2**. This exchange time was ideal such that a certain number of ionizable carboxy-termination at the metal surface ensure the solubility of MPC-**1**,**2** in aqueous medium. Longer exchange times led in fact to extensive replacement of the hydrophilic thioglycolic acid with **1** and **2**, resulting in a clear insolubility of the nanoparticles in aqueous solution. Beside, different molar ratios between the two chromophores resulted in a dominant absorption of either **1** or **2**, not suited for our purposes.

While MPC-**1** exhibits sizes basically similar to those of the carboxy-terminated Pt nanoparticles (*ca.* 1 nm),[13,16] the presence of the porphyrin units in MPC-**1**,**2** encourages interparticle clustering. DLS measurements support the presence of nanoparticle aggregates of *ca.* 10 nm. A similar behavior is also observed in the case of MPC-**2**, which does not contain the NO photodonor units (Fig. 2). These results are not surprising and can be explained on the basis of the tendency of the hydroxyphenyl porphyrin derivatives to self-associate in aqueous medium.[23] The nanoparticle assemblies exhibited good air stability, as confirmed by the negligible variation of the absorption spectrum and the particle size noted after a period of aging in the dark of one week at room temperature.

The absorption characteristics MPC-**1**,**2** together to those of MPC-**1** and MPC-**2** recorded under identical experimental conditions, are presented in Fig. 3. Both the absorption maxima and the spectral shape of **1** and **2** in MPC-**1**,**2** remains almost unaffected if compared to those observed in the case of the nanoparticles containing the single chromophores, MPC-**1** and MPC-**2**. This suggests that despite

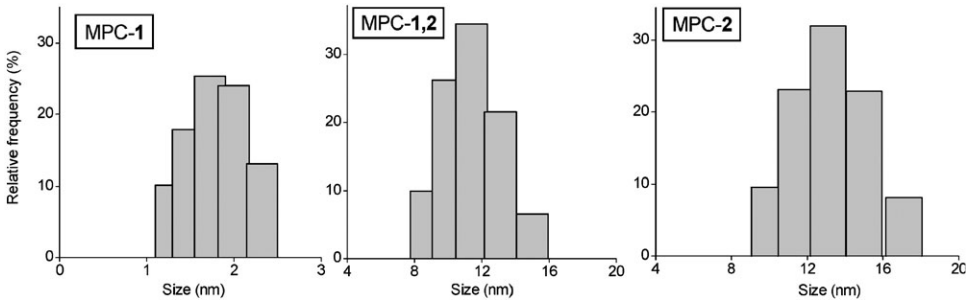


Fig. 2 Size distribution of chromophore-decorated MPCs obtained by DLS measurements in aqueous solution at pH 7.4.

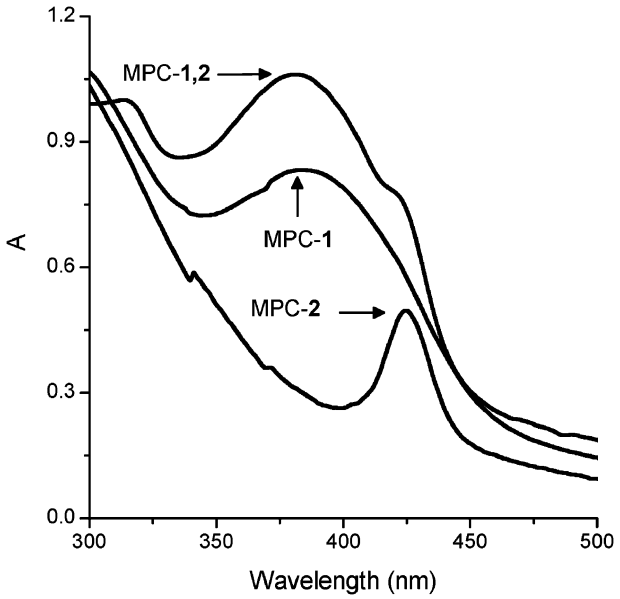


Fig. 3 Absorption spectra of chromophore-decorated MPCs recorded in aqueous solution at pH 7.4.

interparticle aggregation, the perturbation of the frontier molecular orbitals of the two chromophoric units in MPC-**1,2** is negligible.

Fluorescence properties

Fluorescence measurements provided insights into the potential use of these nanoparticles as bright photogenerators of NO. Fig. 4A shows that MPC-**1,2** exhibit the characteristic double band fluorescence arising from the porphyrin fluorogenic center. A quantitative comparison with an optically matched methanol solution of **2** indicates that the fluorescence of the porphyrin is not quenched intensively in the MPC-**1,2** nanoassembly if compared with the unbound fluorophore. In fact we calculated a fluorescence quantum yield $\Phi_F = 0.015$, a value only *ca.* one order of magnitude smaller than that observed for the free fluorophore and much larger with respect to the total suppression of fluorescence observed for porphyrins self-assembled on 2D surfaces.[21] In order to establish possible contribution to the quenching observed by excited state interchromophoric interaction in MPC-**1,2**, we carried out comparative fluorescence experiments with MPC-**2** which, as showed earlier, exhibits similar sizes as MPC-**1,2** but does not contain the NO photodonor unit. As shown in Fig. 4A and

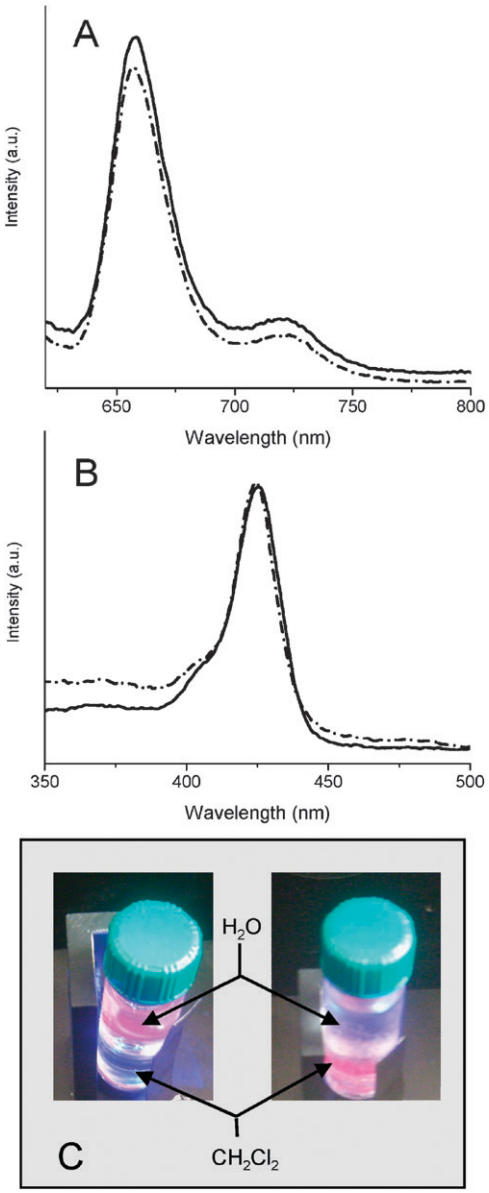


Fig. 4 (A) Fluorescence emission and (B) excitation spectra of MPC-**1,2** (solid line) and MPC-**2** (dotted line) in aqueous solution at pH 7.4; $\lambda_{ex} = 420$ nm; $\lambda_{em} = 650$ nm. (C) Fluorescence images of MPC-**1,2** before (left) and after (right) shaking with a CH_2Cl_2 solution containing 0.1 M TOAB; $\lambda_{ex} = 420$ nm.

B, both emission and excitation spectra of optically matched solutions of the two compounds exhibited virtually identical

spectral profiles, accounting for a behavior of the fluorogenic units independent by the presence of the NO photodonor.

Fig. 4C provides further, clear evidence for the hydrosolubility of MPC-**1,2** and for their potential use as fluorescent probes. As an aqueous solution containing the nanoparticles was mixed with a dichloromethane layer and the double phase sample was irradiated in the fluorimeter compartment, a bright-red fluorescence visible at naked-eye examination and arising exclusively by the aqueous phase was clearly observed (left image). Interestingly, MPC-**1,2** can be easily transferred into organic solvents by using the cationic surfactant tetraoctylammonium bromide (TOAB) as the phase transfer agent. The right hand image in Fig. 4C was taken after shaking with dichloromethane in the presence of 0.1 M TOAB. The bright-red fluorescence arising exclusively by the organic phase, indicates a successful phase transfer process. It should be stressed that the phase transfer experiment provides a further confirmation that the Pt nanoparticles are negatively charged due to the presence of a certain number of carboxylate moieties at their surface. Pure electrostatic interactions between these functional groups and the opposite charged TOAB have been demonstrated to be crucial for the phase transfer process in the case of carboxy-modified gold and platinum nanoparticles[24,25] as well as in the case of our carboxy-terminated Pt nanoparticles not containing the chromogenic centers.[16]

Photorelease of NO

The final part of this work was dedicated to prove that MPC-**1,2** retains the NO photoreleasing properties. The most convenient methodology to demonstrate the NO generation from the nanoassembly is the direct and in real-time monitoring of this radical species. To this end, we have used an ultrasensitive NO electrode, which directly detects NO, with nM resolution, by an amperometric technique. The results illustrated in Fig. 5 provide evidence that MPC-**1,2** are stable in the dark but generate NO at nanomolar level upon illumination with visible light. The release process is strictly dependent by the external light inputs, as confirmed by the linear NO release which promptly stops as the light is turned off and restarts as the illumination is turned on again. A rate of release of *ca.* 0.9 nM s^{-1}, corresponding to a quantum yield for the NO release $\Phi \cong 2 \times 10^{-3}$ can be estimated from the linear portions of the graphic.

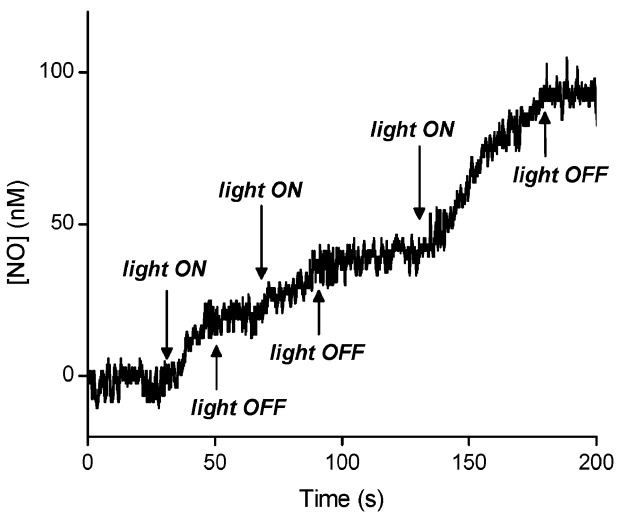
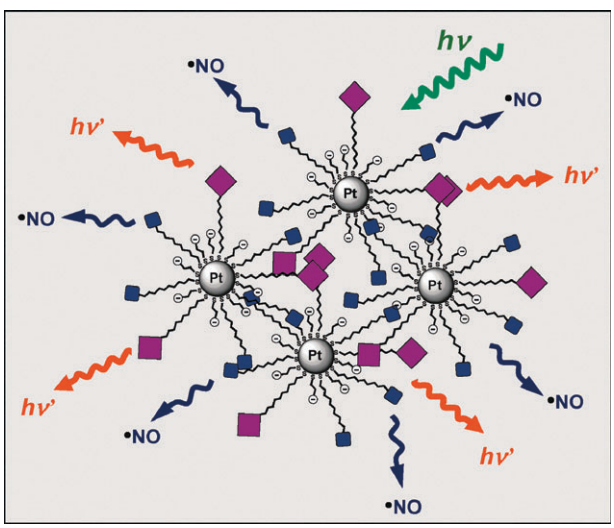


Fig. 5 NO release upon 400 nm irradiation of MPC-**1,2** in aqueous solution at pH 7.4.

Conclusions

We have reported a successfully design and fabrication of functional platinum nanoparticles integrating two photoresponsive units. The introduction of the porphyrin fluorophore at the surface of the metal nanoparticles induces the formation of nanoparticle assemblies of *ca.* 10 nm, which exhibit a bichromophoric behavior upon light excitation. In fact they combine good fluorescence properties with the ability to deliver NO under the exclusive control of light stimuli, as pictorially sketched in Scheme 2. The photoresponse observed accounts for a predominance of independent photoresponsive centers in the nanoassemblies over non-photoactive species. This is probably the result of negligible excited state inter- and intra-chromophore interactions within the nanoparticles and reduced quenching effects by the metal core. These hybrid nanosystems satisfy some indispensable criteria for potential biological applications such as water solubility under physiological conditions, small sizes, dark stability, visible light-regulated release of NO and satisfactory fluorescence yield, this latter a powerful tool for mapping the localization in bio-environments. In this view, MPC-**1,2** represent potentially appealing *bright point sources of NO* to be tested in the emerging field of nanomedical research.



Scheme 2 Idealized view of the MPC-**1,2** bifunctional assemblies.

Acknowledgements

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